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EXAMINER

NGUYEN, DAVE TRONG

ART UNIT	PAPER NUMBER
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1632

DATE MAILED: 03/09/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/996,838

Applicant(s)

HOFLAND ET AL.

Examiner

Dave T. Nguyen

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 09 December 2004.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,7-11,14,15,18 and 19 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1,7-11,14,15,18 and 19 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

Claim 6 has been canceled, claims 1, 7-9, 14, and 15 have been amended by the amendment filed December 9, 2004.

Claims 2-5, 12, 13, 16, 17 have been withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected claimed invention.

Claims 1, 7-11, 14, 15, 18, 19 are pending for examination.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made

to a person having ordinary skill in the art to which said subject matter pertains.

Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 7-11, 14-15, 18, 19 are rejected under 35 USC 102(e), as being anticipated by, or in the alternative, under 35 USC 103, as being unpatentable over Monahan (US 6,379,966 B2).

The claims are readable on an aqueous solution comprising a DNA/polymer complex, wherein one or more cationic head groups of a polymer contained in the DNA/polymer complex is modified by a reaction with citraconic acid anhydride or N-hydroxysuccinimide ester based reagent.

Monahan teaches the same throughout the disclosure, such as the abstract, claims 1, 4, 5, column 4, lines 14-63, column 5 bridging column 6, column 6, line 14-48, column 11, lines 20-65, column 15, line-38, column 23, lines 55-65, column 25, lines 37-

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46, particularly column 24, lines 55-65.

Regarding the main inventive concept of ensuring that a complex composed of a polymer and a DNA has a negative zeta potential prior to a cell delivery protocol in an intravascular environment, the abstract, for example, states:

Disclosed is a complex for providing nucleic acid expression in a cell. A polynucleotide and a polymer are mixed together to form the complex wherein the zeta potential of the complex is not positive. Then the complex is delivered to the cell wherein the nucleic acid is expressed.

Regarding a description of polymeric carriers, column 4 states:

A polymer is a molecule built up by repetitive bonding together of smaller units called monomers. In this application the term polymer includes both oligomers which have two to about 80 monomers and polymers having more than 80 monomers. The polymer can be linear, branched network, star, comb, or ladder types of polymer. The polymer can be a homopolymer in which a single monomer is used or can be copolymer in which two or more monomers are used. Types of copolymers include alternating, random, block and graft.

One of our several methods of nucleic acid delivery to cells is the use of nucleic acid-polycations complexes. It was shown that cationic proteins like histones and protamines or synthetic polymers like polylysine, polyarginine, polyornithine, DEAE dextran, polybrene, and polyethylenimine are effective intracellular delivery agents while small polycations like spermine are ineffective.

A teaching of employing a targeting ligand is disclosed on column 5 bridging column 6.

Regarding the "recharging" concept, wherein a resulting particle with a net negative charge, column 11 states:

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(glutathione) found in the cell. Negatively charged polymers can be fashioned in a similar manner, allowing the condensed nucleic acid particle (DNA+polycation) to be "recharged" with a cleavable anionic polymer resulting in a particle with a net negative charge that after reduction of disulfide bonds will release the polynucleic acid. The reduction potential of the disulfide bond in the reducible co-monomer can be adjusted by chemically altering the disulfide bonds environment. This will allow the construction of particles whose release characteristics can be tailored so that the polynucleic acid is released at the proper point in the delivery process.

Column 15, lines 26-65 also disclose the use of a reactive group such as N-Hydroxysuccinimide esters or citraconic anhydride for the making a cleavable anionic polymers, which then can be employed to be coupled to a targeting ligand and/or DNA/polycation complexes:

Cleavable anionic polymers can be designed in much the same manner as the cationic polymers. Short, multi-valent oligopeptides of glutamic or aspartic acid can be synthesized with the carboxy terminus capped with ethylene diamine. This oligo can then be incorporated into a bulk polymer as a co-monomer with any of the amine reactive disulfide containing crosslinkers mentioned previously. A preferred crosslinker would make use of NHS esters as the reactive group to avoid retention of positive charge as occurs with imidates. The cleavable anionic polymers can be used to recharge positively charged particles of condensed polynucleic acids.

Regarding an advantage of employing of an exterior layer being negatively charge in DNA/polymeric particles, wherein the layer covers the DNA complex so as to make the delivery particle negatively charged, Column 23 discloses:

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To increase the stability of DNA particles in serum, we have added to positively-charged DNA-polycation particles polyanions that form a third layer in the DNA complex and make the particle negatively charged. To assist in the disruption of the DNA complexes, we have synthesized polymers that are cleaved in the acid conditions found in the endosome, pH 5-7. We also have reason to believe that cleavage of polymers in the DNA complexes in the endosome assists in endosome disruption and release of DNA into the cytoplasm.

Regarding the advantages of employing negatively charged complexes using non-cleavable polymers, column 28 discloses:

Many cationic polymers such as histone (H1, H2a, H2b, H3, H4, H5), HMG proteins, poly-L-lysine, polyethyleneimine, protamine, and poly-histidine are used to compact polynucleic acids to help facilitate gene delivery in vitro and in vivo. A key for efficient gene delivery using prior art methods is that the non-cleavable cationic polymers (both in vitro and in vivo) must be present in a charge excess over the DNA so that the overall net charge of the DNA/polycation complex is positive. Conversely, using our intravascular delivery process having non-cleavable cationic polymer/DNA complexes we found that gene expression is most efficient when the overall net charge of the complexes are negative (DNA negative charge > polycation positive charge). Tail vein injections using cationic polymers commonly used for DNA condensation and in vitro gene delivery revealed that high gene expression occurred when the net charge of the complexes were negative.

Specific species of DNA, which include antisense and those that encode therapeutic proteins, are disclosed on column 6.

To the extent that the claims are readable on specific embodiments, which include an incorporation of a targeting or fusogenic peptide to an N-hydroxysuccinimide, wherein the reagent can be added to the exterior of and within a polymer/DNA complex, it would have been obvious for one of ordinary skill in the art to react to a N-Hydroxysuccinimide ester containing targeting/fusogenic ligand to the surface of the a

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polymer /DNA complex. One of ordinary skill in the art would have been motivated to couple covalently to a N-Hydroxysuccinimide ester containing targeting/fusogenic ligand to the surface of a polymer/DNA complex because Monahan teaches that targeting/fusogenic ligands can be incorporated to the surface of a DNA carrier in order to increase the utility of the carrier for targeted delivery of the DNA, and by having a N-Hydroxysuccinimide ester in a targeting ligand such as peptide ligand, one would also ensure an the overall net negative charge on the surface of the modified polymer/DNA complex, and such coupling would be able to be cleaved within a transfected cell (column 24 to column 25), as taught as being advantageous by the combined cited references. One of ordinary skill in the art would have expected from the teaching of Monahan that expression is most efficient as long as the overall net charge of the complexes is negative charged, and that the DNA would then be released intracellularly for expression.

Thus, the claims are anticipatory, or in the alternative, are *prima facie* obvious.

Applicant's assertion (page 7) has been considered by the examiner but is not found persuasive. Specifically, applicant asserts on page 7 that the step of reacting a reagent with the cationic head groups of the polycation is not taught anywhere in Monahan. However, Column 23 discloses:

To increase the stability of DNA particles in serum, we have added to positively-charged DNA-polycation particles polyanions that form a third layer in the DNA complex and make the particle negatively charged. To assist in the disruption of the DNA complexes, we have synthesized polymers that are cleaved in the acid conditions found in the endosome, pH 5-7. We also have reason to believe that cleavage of polymers in the DNA complexes in the endosome assists in endosome disruption and release of DNA into the cytoplasm.

Such teaching, regardless whether Monahan is silent on the elaboration of a reaction between the cationic head groups of the polycations with the polyanionic molecules, does show that the polyanions would bind to the polycationic head groups by electrostatic bondinngs as evidenced by the fact that the cationic head groups and the polyanions are opposite in charges.

Applicant further asserts that by citing column 25 of Monahan, the making of such citraconylpoly-L-lysine is completely different from that of the 'amended' claimed invention. In response, the examiner acknowledges that such citation is no longer applicable to the currently amended claimed invention. However, the teaching of Monahan as a whole anticipates and/or renders the claimed invention obvious. By teaching alternatively that in order to increase the stability of DNA particles in serum, a person of ordinary skill in the art could also have added to a polycation-DNA complex a polyanionic molecule in order to make the complex as a whole anionic, Monahan thereby teaches the amended claimed invention. Applicant appears to argue that either Monahan teaches away from the claimed invention and/or is not enabling for the teaching of adding a polyanion to a polycation/DNA complex. However, such is not found persuasive because the presence of an alterative teaching does not constitute a teaching-away element, nor is it apparent such teaching of an elementary or basic science of charged interactions is considered unpredictable to a person of ordinary skill in the art of polymer-chemistry at the time the invention was made.

Claims 1 is rejected under 35 USC 102(e) as being anticipated by Semple (US Pat No. 6,287,591 B1).

The claims are readable on an aqueous solution comprising a DNA/cationic lipid complex, wherein one or more cationic head groups of the complex on the surface of the lipid particles are modified by a reagent containing buffer so as to form modified DNA/cationic lipid complex having an overall net neutral surface. Semple teaches the

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same on column 9. More specifically, Column 9 states:

The methods and composition of the invention make use of certain lipids which can be present in both a charged and an uncharged form. For example, amino lipids which are charged at a pH below the pK_a of the amino group and substantially neutral at a pH above the pK_a can be used in a two-step process. First, lipid vesicles can be formed at the lower pH with (cationic) amino lipids and other vesicle components in the presence of nucleic acids. In this manner the vesicles will encapsulate and entrap the nucleic acids. Second, the surface charge of the newly formed vesicles can be neutralized by increasing the pH of the medium to a level above the pK_a of the amino lipids present, i.e., to physiological pH or higher. Particularly advantageous aspects of this process include both the facile removal of any surface adsorbed nucleic acid and a resultant nucleic acid delivery vehicle which has a neutral surface. Liposomes or lipid particles having a neutral surface are expected to avoid rapid clearance from circulation and to avoid certain toxicities which are associated with cationic liposome preparations.

Column 10 further discloses that

As used herein, the term "amino lipid" is meant to include those lipids having one or two fatty acid or fatty alkyl chains and an amino head group (including an alkylamino or dialkylamino group) which is protonated to form a cationic lipid at physiological pH (see FIG. 2A). In one group of

Thus, Semple teaches that by modifying the surface of DNA/cationic lipid particles containing formulation, the particles would resist degradation from *in vivo* circulation and not produce certain toxicities, which are associated with cationic liposome preparations. As such, the claims are anticipatory.

Applicant further argues on page 9 that Semple does not teach the make and use of a reagent as recited in the claims. However, a reagent containing buffer so as to

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adjust the charges would meet the generic limitation. Thus, the rejection remains proper.

Claims 1, 7-11, 14, 18, 19 are rejected under 35 USC 103(a) as being unpatentable over Semple (US Pat No. 6,287,591 B1) taken with Trubetskoy (US 2003/0026841 A1, claiming priority to provisional application 60/174,132, filed 12/31/99, wherein a copy of the provisional application is attached) and Monahan (US 6,379,966 B2).

The claims are readable on an aqueous solution comprising a DNA/cationic lipid complex, wherein one or more cationic head groups of the complex is modified by a reagent such as a buffered solution containing citraconic anhydride or N-hydroxysuccinimide ester so as to form modified DNA/cationic lipid complex having an overall net neutral or negative charge.

Semple teaches the same on column 9. More specifically, Column 9 states:

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The methods and composition of the invention make use of certain lipids which can be present in both a charged and an uncharged form. For example, amino lipids which are charged at a pH below the pK_a of the amino group and substantially neutral at a pH above the pK_a can be used in a two-step process. First, lipid vesicles can be formed at the lower pH with (cationic) amino lipids and other vesicle components in the presence of nucleic acids. In this manner the vesicles will encapsulate and entrap the nucleic acids. Second, the surface charge of the newly formed vesicles can be neutralized by increasing the pH of the medium to a level above the pK_a of the amino lipids present, i.e., to physiological pH or higher. Particularly advantageous aspects of this process include both the facile removal of any surface adsorbed nucleic acid and a resultant nucleic acid delivery vehicle which has a neutral surface. Liposomes or lipid particles having a neutral surface are expected to avoid rapid clearance from circulation and to avoid certain toxicities which are associated with cationic liposomal preparations.

Column 10 further discloses that

As used herein, the term "amino lipid" is meant to include those lipids having one or two fatty acid or fatty alkyl chains and an amino head group (including an alkylamino or dialkylamino group) which is protonated to form a cationic lipid at physiological pH (see FIG. 2A). In one group of

Thus, Semple teaches that by modifying the surface of DNA/cationic lipid particles containing formulation, the particles would resist degradation from *in vivo* circulation and not produce certain toxicities, which are associated with cationic liposome preparations. Therapeutic DNA sequences are disclosed throughout columns 14-16.

Semple does not teach the use of a buffered solution containing citraconic anhydride or N-hydroxysuccinimide ester for charge modification, nor does Semple teach that the surface of the lipid particles have an overall net negative charge.

However, at the time the invention was made, on par. 52 on page 5 (also see page 1 of the provisional application). Trubetskoy teaches that at the time the invention was made, a recharging process can be applied to a cationic lipid/DNA complex in a typical gene delivery formulation, thereby enhancing the efficiency of gene transfer *in vivo*.

In addition, Monahan teaches the use of a reactive group such as N-Hydroxysuccinimide esters or citraconic anhydride as functional groups for charge modifications. Specifically, Monahan teaches the use of the functional or reactive groups for the making a cleavable N-Hydroxysuccinimide esters or citraconic anhydride based anionic polymer, which then can be employed for coupling to DNA/polycation complexes:

Cleavable anionic polymers can be designed in much the same manner as the cationic polymers. Short, multi-valent oligopeptides of glutamic or aspartic acid can be synthesized with the carboxy terminus capped with ethylene diamine. This oligo can be incorporated into a bulk polymer as a co-monomer with any of the amine reactive disulfide containing crosslinkers mentioned previously. A preferred crosslinker would make use of NHS esters as the reactive group to avoid retention of positive charge as occurs with imidates. The cleavable anionic polymers can be used to recharge positively charged particles of condensed polynucleic acids.

Regarding an advantage of employing of an exterior layer being negatively charge, wherein the layer covers the DNA complex so as to make the delivery particle negatively charged, Column 23 of Monahan discloses:

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To increase the stability of DNA particles in serum, we have added to positively-charged DNA-polycation particles polyanions that form a third layer in the DNA complex and make the particle negatively charged. To assist in the disruption of the DNA complexes, we have synthesized polymers that are cleaved in the acid conditions found in the endosome, pH 5-7. We also have reason to believe that cleavage of polymers in the DNA complexes in the endosome assists in endosome disruption and release of DNA into the cytoplasm.

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The use of citraconic anhydride as a functional or reactive group is disclosed column 25, lines 27-36.

Regarding the advantages of employing negatively charged complexes using non-cleavable polymers, column 28 discloses:

Many cationic polymers such as histone (H1, H2a, H2b, H3, H4, H5), HMG proteins, poly-L-lysine, polyethyleneimine, protamine, and poly-histidine are used to compact polynucleic acids to help facilitate gene delivery in vitro and in vivo. A key for efficient gene delivery using prior art methods is that the non-cleavable cationic polymers (both in vitro and in vivo) must be present in a charge excess over the DNA so that the overall net charge of the DNA/polycation complex is positive. Conversely, using our intravascular delivery process having non-cleavable cationic polymer/DNA complexes we found that gene expression is most efficient when the overall net charge of the complexes are negative (DNA negative charge > polycation positive charge). Tail vein injections using cationic polymers commonly used for DNA condensation and in vitro gene delivery revealed that high gene expression occurred when the net charge of the complexes were negative.

Thus, it would have been obvious to one of ordinary skill in the art at the time the invention made that a charge modification or reversing process is a necessary step to enhance an *in vivo* stability and gene transfer efficiency of a cationic lipid/DNA particles having a positively charge surface, as evidenced by the teachings of all of the cited references. One of ordinary skill in the art then would have been motivated to further

modify the surface of a cationic lipid/DNA complex such as those employed in Semple or known in the prior art so as to ensure that the surface of these charged lipid/DNA particles have an overall neutral or negative charges. One of ordinary skill in the art would have been motivated to make a charge modification on the surface of the cationic lipid/DNA particles with any known reagent because by having the overall neutral or negative charge on the surface of the lipid particles, the particles would have more stability, entrap more DNA, resist degradation during its *in vivo* circulation, and provide an enhanced gene transfer efficiency, as evidenced by the teachings of Trubetskoy and Monahan.

One of ordinary skill in the art would also have been motivated to employ any known reagent, such as a buffer containing N-Hydroxysuccinimide esters or citraconic anhydride, which is conventionally employed in the prior art for charge modification, for charge modification of the surface of any amino lipid/DNA particles or cationic head group containing lipid/DNA particles. One of ordinary skill in the art would have been motivated to do so because both Semple teaches that a buffered solution can be used to neutralize the positive charges present on the surface of a lipid/DNA complex, and because Trubetskoy teaches that an addition of polyanionic molecules would enhance the transfer activity of a DNA/cationic lipid complex. One of ordinary skill in the art would have expected that N-Hydroxysuccinimide esters or citraconic anhydride are suitable reactive groups because Monahan teaches the use of the reagents in a charge modification of a cationic molecule such as a cationic amino group, and further teaches that gene expression is most efficient when the overall net charge of the complexes is

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negative. One would have a reasonable expectation of success of being able to efficiently deliver and express a DNA of choice *in vivo* as long as the overall net charge of the complexes as a result of a charge modification is neutral or negative.

To the extent that the claims are readable on specific embodiments, which include an incorporation of a targeting ligand to an N-hydroxysuccinimide, wherein the reagent can be added to the exterior of a lipid/DNA complex, it would have been obvious for one of ordinary skill in the art to react to a N-Hydroxysuccinimide ester containing targeting or fusogenic ligand to the surface of the a lipid/DNA complex. One of ordinary skill in the art would have been motivated to couple covalently a N-Hydroxysuccinimide ester containing targeting ligand to the surface of a lipid/DNA complex because Monahan teaches that targeting ligands can be incorporated to the surface of a DNA carrier in order to increase the utility of the carrier for targeted delivery of the DNA, and by having a N-Hydroxysuccinimide ester in a targeting ligand such as peptide ligand, one would also ensure an the overall net negative charge on the surface of the modified lipid/DNA complex, as taught as being advantageous by the combined cited references.

Thus, the claims as a whole are *prima facie* obvious.

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE **THREE MONTHS** FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT

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MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN **SIX MONTHS** FROM THE DATE OF THIS FINAL ACTION.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner *Dave Nguyen* whose telephone number is **571-272-0731**.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *Ram Shukla*, may be reached at **571-272-0735**.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Central Fax number, which is **571-273-8300**.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Dave Nguyen
Primary Examiner
Art Unit: 1632



**DAVE TRONG NGUYEN
PRIMARY EXAMINER**